REMARKS

Information Regarding the Invention

The present invention concerns products and methods for use in predicting the function of proteins. The inventors have discovered that it is not necessary to accurately predict the overall three-dimensional structure of a particular protein of interest in order to identify its function. Instead, prediction of biological function using the products and methods described and claimed herein requires only an initial approximation of the three-dimensional orientation of atoms within certain amino acid residues determined to be responsible for the particular function of the protein under investigation. *See*, *e.g.*, Specification at page 11.

"Functional site descriptors" of the invention define a spatial configuration of atoms and/or groups of atoms within a protein functional site that corresponds to a biological function. In creating these functional site descriptors, the invention initially makes use of existing structural or predicted structural information to create a functional site descriptor, for example, computationally derived models of three dimensional protein structure (including inexact models) produced from deduced primary amino acid sequences. *See*, *e.g.*, Specification at page 22; *see also*, *e.g.*, page 75, lines 14 to 17 (functional site residues can be chosen "based on an analysis of existing structures or other information relating to the particular biological function under consideration") and Figure 9. Such models may be generated by a variety of techniques including, for example, by application of an *ab initio* folding program, a threading program, a homology modeling program, or another protein structure prediction algorithm. In other words, functional site descriptors are defined based on various constraints such as atomic or molecular geometry and residue identity which, while derivable from functional sites of proteins of known,

high-resolution structure, may also be derived from predicted structures, including inexact protein models. *See*, *e.g.*, Specification at page 31. Accordingly, in alternative aspects of the invention the operation of determining a set of geometric constraints of a functional site correlated with a biological function of a protein comprises receiving said set of geometric constraints from at least one of the group of a data set of predetermined geometric constraints or from user input. *See*, *e.g.*, Specification at page 27.

Functional site descriptors according to the invention can be produced, for example, by the following steps outlined in Figure 4. Initially, functionally and/or structurally important residues are identified (step 212) by, for example, a search of the scientific literature regarding a particular biomolecule to provide information about the residues that are or may be important for a particular biological function. *See*, *e.g.*, Specification at page 37. Next, one, and alternatively more, proteins are selected that possess the particular function and for which an experimentally determined three dimensional structure (in one aspect, a high resolution structure) is known. The putative functionally important residues are identified in the known three-dimensional structure(s), and the relative geometries (*e.g.*, distances, angles) between atoms or group of atoms, for example, the α-carbons of each of the functionally important amino acids of a protein, are recorded. *See*, *e.g.*, Specification at pages 37-38. *See also* Figures 2-5.

A functional site descriptor typically comprises a set of geometric constraints for one or more atoms in each of the amino acid residues used to define a functional site of a protein. In one aspect of the invention, one or more of these atoms is an amide nitrogen, a α-carbon, a carbonyl carbon, or a carbonyl oxygen within a polypeptide backbone, a β-carbons within an

amino acid residue, and/or a pseudoatom. (Exemplary pseudoatoms are centers of mass, such as may be derived from at least two atoms, such as two or more atoms from one amino acid residue or two or more atoms from at least two amino acid residues of the protein. *See*, *e.g.*, Specification at page 25.) In one aspect of the invention, at least one of these atoms is an amide nitrogen, an α-carbon, a β-carbon, or a carbonyl oxygen within a polypeptide backbone. *See*, *e.g.*, Specification at page 23.

In various embodiments, a functional site descriptor represents 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues (or sets of residues) that are used to define a functional site. While a functional site descriptor may include one or more identity constraints with respect to any amino acid, such constraints will often make reference to naturally occurring amino acids including the L-amino acids Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val. *See*, *e.g.*, Specification at pages 23-24. The geometric constraints of a functional site descriptor, in alternative aspects of the invention an atomic position specified by a set of three dimensional coordinates, an interatomic distance (or range of interatomic distances), and/or an interatomic bond angle (or range of interatomic bond angles).

When a geometric constraint refers to atomic position, reference is typically made to a set of three dimensional coordinates. In one aspect of the invention, such constraints relate to RMSDs, particularly those that allow the atomic position to vary within a preselected RMSD, for example, by an amount of less than about 3 Å, less than about 2.5 Å, less than about 2.0 Å, less than about 1.5 Å, and less than about 1.0 Å. Other geometric constraints concern interatomic distances, in one aspect interatomic distance ranges, or interatomic bond angles range, in one aspect interatomic bond angle ranges. In some embodiments, a functional site descriptor can

also include one or more conformational constraints that refer to the presence of a particular secondary structure, for example, a helix, or location, for example, near the amino or carboxy terminus of a protein. *See*, *e.g.*, Specification at page 24.

Once a constraint set has been adopted as a functional site descriptor for a particular biological function, it may then be tested to determine whether it misses or fails to identify any protein within experimentally determined or other structures known or suspected to exhibit the particular biological function under investigation. If so, the structure of the missed protein, particularly the structure of the functional site correlated with the desired biological function, is analyzed. One or more of the constraints comprising the functional site descriptor may then be modified or relaxed so that the biomolecule exhibiting the function is correctly identified upon re-testing. "Relaxation" of a functional site descriptor constraint or parameter, *e.g.*, the distance between the α-carbons of two functionally important amino acids, refers to the range of numbers embodied by the particular parameter. In one aspect of the invention if one or more or all members of the constraint set are adjusted to allow, in the case of spatial constraints (*e.g.*, distance constraints, bond angle constraints, *etc.*), the greatest possible latitude between relevant atoms (or groups of atoms, *etc.*) without leading to the identification of proteins lacking the desired function but exhibiting a related structure. *See*, *e.g.*, Specification at pages 38-41. *See also* Figure 7.

In one aspect functional site descriptors are functional site descriptors that are three atom functional site descriptors, four atom functional site descriptors, five atom functional site descriptors, six atom functional site descriptors, seven atom functional site descriptors, eight

atom functional site descriptors, nine atom functional site descriptors, ten atom functional site descriptors, eleven atom functional site descriptors, twelve atom functional site descriptors, thirteen atom functional site descriptors, fourteen atom functional site descriptors, and fifteen atom functional site descriptors. *See, e.g.*, Specification at page 25. *See also* Figures 6 and 8.

The application describes, for example, certain embodiments referred to as "9-distance" functional site descriptors. *See, e.g.*, Specification at page 24. Thus, in various active site descriptors according to the invention, a nine-distance data set that describes nine distances among various atoms within amino acid residues and adjacent residues may be utilized. FIG. 6C is a diagram illustrating an example of nine distances for the example residues illustrated in FIG. 6B. FIG. 6C illustrates residue pairings for purposes of determining distances between α-carbon atoms of amino acid residues in a hypothetical active site (the residue pairs of this "9-distance" set of geometric constraints depicted being: 84-142, 84-3, 3-142, 83-3, 85-3, 141-84, 143-84 2-84, and 4-84). More or fewer geometric constraints can be utilized.

Additionally, the invention provides for adjustment of these geometries to define a functional site descriptor that is broad enough to encompass active sites exhibiting the same functionality yet not so broad as to encompass active sites that do not have the desired functionality. As shown in step 272 of FIG. 5, the geometry of a determined active site descriptor may be broadened, for example, by adding a delta, which, in the above hypothetical, is in alternative aspects a plus or minus uncertainty level, or range, in the distances between the residues selected to comprise the functional site descriptor. As a result, this site descriptor is

defined, in part, by a plurality of distances, wherein each distance has associated therewith a level of uncertainty.

In step 274, a functional site descriptor having relaxed geometric parameters is compared with one or more functional sites in the data set of known functional sites to determine if the relaxed descriptor accurately identifies biomolecules in the data set known to have the particular biological function correlated with the descriptor. The functional site descriptor also may be compared with biomolecules known not to exhibit the function associated with that functional site. If the functional site descriptor known to have a specified function matches or compares favorably to only biomolecules known to have the particular function, and not to biomolecules known not to have that function, the geometric parameters (or other parameters comprising the functional site descriptor) can be expanded (or relaxed) further. Once the parameters of the descriptor have been so expanded, the functional site descriptor can be applied again to the data set to determine whether it matches a sufficient number of the existing active sites known to have this function, without encompassing structures that are known not to have this function. This is illustrated by steps 276 and 278 and flow line 280 in FIG. 5. FIG. 7 is an operational flow diagram illustrating a process for adjusting one or more geometric distance parameters of a functional site descriptor according to the invention.

FIG. 8 is a diagram illustrating an example data set for geometric constraints of a "9 distance" functional site descriptor developed in accordance with instant process and representing the active site of phospholipase A2. The data set in FIG. 8 is illustrated in tabular form for ease of description. The rows in FIG. 8 correspond to the distance parameters (written

as average distances plus or minus a standard deviation multiplied by a multiplier (here, 2.0)) of the functional site descriptor (here, for the active site of proteins having phospholipase activity). For the embodiment where nine distances make up the active site, the exemplary nine distances are illustrated by the referenced characters 320A through 320I. The columns in FIG. 8 provide the pertinent data for each residue pair distance. In the FIG. 8 example, these include the average distances for the residue pairs, the standard deviation of these distances among the data set, and the multiplier 326 used to broaden the geometry to the desired breadth. *See also, e.g.*, FIG. 9, which represents an operational flow diagram illustrating a process for creating a functional site descriptor including techniques for training the data set according to one embodiment of the invention, and the Specification at pages 75-76.

The invention also concerns computer program products comprising a computer useable medium having computer program logic recorded thereon for creating a functional site descriptor for use in predicting a biological function of a protein, or that embody functional site descriptors, or direct the use of functional site descriptors. Such computer program products and associated machines are described and claimed in the application. *See also* Figure 11.

Information Regarding the Claims

Independent claim 53 and dependent claims 3, 5-10, 12-14, 16-19, 20, 22, and 61-65 – Pending independent claim 53 and dependent claims 3, 5-10, 12-14, 16-19, 20 and 22 represent a first set of computer program product claims and relate to a computer program product with executable instructions comprising a functional site descriptor. New claim 61 depends from

claim 53, and new dependent claims 62-65 depend from claim 17 (which, in turn, depends from independent claim 53).

Independent claim 45 and dependent claims 46, 48-50, 52 and 66-74 – Pending independent claim 45 and dependent claims 48-50, 52 and 65-74 represent a second set of computer program product claims and relate to a computer program product with executable instructions for creating a functional site descriptor. New dependent claims 66-74 depend directly or indirectly from independent claim 45.

Independent claim 54 and dependent claims 75-90 – Pending independent claim 54 and new dependent claims 75-90 represent a first set of computer implemented method claims that relate to determining a functional site descriptor.

Independent claim 56 – Pending independent claim 56 represents a second computer-implemented method for defining a functional site descriptor.

Independent claims 58 and 59 – Pending independent claims 58 and 59 represent computer system claims.

Independent claim 91 and dependent claims 92-102 – New independent claim 91 and dependent claims 92-102 relate to methods for creating a functional site descriptor.

Independent claim 103 – New independent claim 103 relates to computer system for determining the existence of a functional site in a test protein.

Independent claim 104 – New independent claim 104 relates to a machine having a memory that contains data representing a functional site descriptor generated by the methods of various preceding claims.

Independent claim 105 and dependent claims 106 and 107 – New independent claim 105 relates to one embodiment of the invention relating to the creation of, for example, a nine-geometry active site descriptor. Dependent claims 106 and 107 relate to embodiments referred to as "9-distance" functional site descriptors. In particular, claim 107 defines a method wherein the geometric constraint comprises nine distances between the α-carbons of three amino acids used to define a protein active site and the α-carbons of the amino acids adjacent to each of these three amino acids.

Dependent claims 108-114 – New dependent claims 108-114 relate to certain embodiments of methods, computer program products, computer systems, and machines wherein the functional site of the functional site descriptor is a protein active site, the amino acid residue identity constraint comprises three amino acids used to define the protein active site, and the geometric constraints comprise nine distances between the α-carbons of said three amino acids and the α-carbons of the amino acids adjacent to each of the three amino acids.

All of the claim changes are cosmetic and none raise any issue of patentability. Both before and after the above changes and the addition of new claims, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to

embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as having been altered in any way for any reason related to patentability, a concession that the invention as patented does not reach as far as the original, unamended claim, a surrender of any subject matter as a condition of receiving a patent; and/or, estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for claims comprising identifying or using a functional site using at least one atom from each of about fifteen or fewer amino acid residues can be found, inter alia, on page 25, lines 8 to 19. Support for claims wherein the functional site descriptor is a three-dimensional representation of a protein functional site can be found, inter alia, on page 23, lines 7 to 9.

The June 17, 2002 Office Action

35 USC 112, Second Paragraph

Claims 2-14, 16-20, 22, and 44-60 were rejected under 35 USC §112, second paragraph.

The Examiner asserted that:

> The base claims 45, 53, 54 recite that geometric constraints are to be selected between at least three atoms, which means that there may be more than three atoms selected. The criteria for selection of atoms in the latter case is not clear. The description of the third atom in the claims is different the first two. Consequently, for the embodiments wherein more than three atoms are selected, it is not clear whether the atoms should be as defined for the first/second atom, or as for third atom. Clarification is requested.

June 17, 2002 Office Action, page 3.

The second paragraph of 35 USC §112 requires that a specification include claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Indefiniteness is a question of law, *Carl Zeiss Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1181, 20 USPQ2d 1094, 1101 (Fed. Cir. 1991), and determining whether a claim is indefinite requires an analysis of "whether one skilled in the art would understand the bounds of the claim when read in light of the specification. . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more." *Miles Lab., Inc. v. Shandon Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), *cert. denied*, 114 S. Ct. 943 (1994); *see also Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The purpose of claims is not to explain the technology or how it works, but to state the legal boundaries of the patent grant. A claim is not "indefinite" simply because it is hard to understand when viewed without benefit of the specification. Here, it is plain that the claims are not so lacking in clarity as to be indefinite.

With regard to the first assertion of the Examiner regarding the "criteria for selection of atoms" where more than three atoms are used, the specification, including the figures, contains significant description and exemplification of such criteria. *See, e.g.*, the discussion of identity constraints at page 20 of the Specification, the discussion of functional site descriptors at pages 23-25 of the Specification, as well as the discussions relating to, for example, "9-distance" functional site descriptors noted above. *See also, e.g.*, Figures 2-9. With regard to the second

assertion of the Examiner alleging that the "description of the third atom in the claims is different the first two," applicants note this description is consistent with the specification and, thus, the metes and bounds of the claims are understandable and the claims are not indefinite.

Although it is the law that claims may use language that those skilled in the art understand without the need for explicit, detailed definitions in the written description, *see, e.g.*, *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58, 220 USPQ 303, 315-16 (Fed. Cir. 1983), such detail is provided in the instant specification. Thus, Applicants request that the Examiner reconsider and withdraw this rejection.

As noted above, none of the amendments to any claims in this application, or the presentation of new claims, may be interpreted as limiting in any way the scope of any issued claims.

35 USC 101

Pending claims 2-14, 16-20, 22, and 45-52 and 53 were rejected under 35 USC 101 as allegedly directed to non-statutory subject matter. Pending claims 44 and 54-60 relating to a computer implemented method for determining a functional site descriptor are thus free of this rejection and constitute statutory subject matter within Section 101 (although claims 44, 51, 55, 57 and 60 have been cancelled without prejudice as a result of the recasting of various claims as set forth herein). It will also be clear that, while certain of the above-listed claims have been cancelled or modified, none have been cancelled or modified for any reason related to this rejection.

Claims 16-20 and 22 were rejected as allegedly drawn to "a 'functional site descriptor' and libraries of said descriptors." These claims all relate to computer program products and all depend directly or indirectly from independent claim 53. The Examiner bases his rejection on the allegation that claims 16-20 and 22 are directed to "descriptive material per se."

The Examiner also rejected independent claim 53 (and dependent claims 2-14), as well as independent claim 45 (and dependent claims 46-52). Each of these claims is also directed to a computer program product. With regard to claims 2-14 and 45-53, the Examiner alleges that the "invention as a whole is directed to a mere program listing, i.e., it is descriptive material *per se*." The Examiner further alleges that this material "cannot exhibit any functional interrelationship with the way in which computer processes are performed" and thus "does not constitute a statutory process." This rejection is traversed.

As noted above, there are several different types of computer program product claims in this case. They include claims to a computer program product for creating a functional site descriptor (independent claim 45), a computer program product embodying a functional site descriptor for use, *e.g.*, in identifying a protein functional site (independent claim 53), methods for determining or defining functional site descriptors (independent claims 54 and 56), and a computer system (independent claims 58 and 59). None of these claims is a "mere program listing" and each represents statutory subject matter under Section 101 of the patent law.

With regard to the Examiner's reference to alleged "descriptive material," page 8 of the PTO's "Examination Guidelines for Computer-Related Inventions" discusses functional versus

non-functional "descriptive material." According to the Guidelines, the former represents patentable subject matter within the meaning of 35 USC 101, while the latter is not:

> Descriptive material can be characterized as either "functional descriptive material" or "non-functional descriptive material." In this context, "functional descriptive material" consists of data structures and computer programs which impart functionality when encoded on a computer-readable medium. "Non-functional descriptive material" includes but is not limited to music, literary works and a compilation or mere arrangement of data [footnote 27 omitted].

Applicants' claims are not directed to music, literary works and a compilation or mere arrangement of data. Rather, they include claims to computer programs that plainly impart functionality when encoded on a computer-readable medium. *See*, *e.g.*, claims 45 and 53, which are directed to computer program products. The computer program products comprise "a computer readable medium having executable instructions representing a computer program recorded thereon," and both before and after amendment represent patentable subject matter within the meaning of 35 USC 101.

Indeed, the Guidelines state specifically that, "When functional descriptive material is recorded on some computer-readable medium it becomes structurally and functionally interrelated to the medium and will be statutory in most cases [footnote 28 omitted]."[1] Patents to computer program products "including a computer readable medium having executable

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[1] *See also* page 13 of the PTO's "Examination Guidelines for Computer-Related Inventions" reiterates that computer "claimed computer-readable medium encoded with a data structure defines structural and functional interrelationships between the data structure and the medium which permit the data structure's functionality to be realized, and is thus statutory."

instructions representing a computer program recorded thereon" have long been issued by the PTO.[2] Applicants respectfully request that this rejection be reconsidered and withdrawn.

As noted above, none of the amendments to any claims that are the subject of this rejection, or the presentation of new claims, may be interpreted as limiting in any way the scope of any issued claims.

35 USC 102 and 103

Wallace *et al*.

Pending claims 2-14, 16-20, 22, and 44-60 were rejected under 35 USC 102(b) as allegedly anticipated by or, in the alternative, under 35 USC 103(a) as allegedly obvious over Wallace *et al*.

The Examiner makes two contentions in response to Applicants' argument regarding Wallace *et al*. First, the Examiner asserts that the Wallace *et al*. article

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[2] *See, e.g.*, U.S. Pat. No. 6,446,259 issued September 3, 2002, to Bevin R. Brett (Compaq Computer Corporation) for "System and method for generating an object structure at run time in an object-oriented programming language," which claims, for example:

> 5. A ***computer program product including a computer readable medium having executable instructions representing a computer program recorded thereon***, said executable instructions comprising:
>
> program code for determining a base class offset between a virtual base class and a derived class, said derived class being derived from said virtual base class;
>
> program code for generating a base table for said derived class, said base table including said base class offset; and
>
> program code for generating other program code for being executed at run time to create at run time a virtual function table and an adjusting function for said virtual base class, said adjusting function being operable to generate a pointer, based upon contents of the base table, to the derived class object when executed, the virtual function table containing another pointer to the adjusting function.

> teaches that distances are measured between Asp and Ser residues (functional oxygens of their side chain in the preferred embodiment) and His residue for which the location of set point [sic] is not specified and thus can be either a side chain ring or a backbone atom (see, for example, discussion of relative position of Ser214 towards "the backbone of His", p. 1008, line 8).

June 17 Office Action, page 6. In contrast, Applicants note that the set point of the His residue is not a single point but is the entire His side chain. This is indicated in at least three different places in Wallace *et al.*:

1. page 1004, paragraph 1 under "Derivation of 3D templates," which states that the "planar ring of the His [side chain]" is used as the "common reference frame" (Figure 4);

2. page 1005, paragraph 1 under "The Ser-His-Asp templates," which states that the "functional template" uses the "3D coordinates of the reference His side chain plus the two functional oxygens on the Ser and Asp residues"; and,

3. Table 3 on page 1005, which specifies that the functional template includes all of the side chain ring atoms of the His residue.

See also Figure 4. Thus, the His reference atom(s) were not "either a side chain ring or a backbone atom," as asserted by the Examiner. The His reference atoms were all side chain atoms.

The portion of page 1008 of the Wallace *et al.* article quoted by the Examiner that refers to "the backbone of His" does not contradict these statements. There the authors merely refer to an observation made from their findings and, as a result, propose an alternative role for the interaction between Ser214 and His57 from what had been presented in the literature. Previously, it had been suggested that Ser214 plays "an electrostatic stabilization role" in catalysis. Based on their data, Wallace *et al.*, suggest instead that the role of Ser214 is to form a series of hydrogen bonds with the backbone of the His57, thus positioning the side chain of His57 to be in the optimal orientation to

interact with the Asp 102 side chain. It is not a description of how one may define a "functional template."

Secondly, the Examiner states that "the Wallace method is not limited to the preferred embodiment describing particular residues of particular enzyme [sic]," and that "the instant claims are not drawn to 'catalytic' or 'non-catalytic' atoms; all the claims require is that atoms belong to different residues." Applicants' pending and newly added claims all include reference to one or more backbone atoms or, for example, to nine or more atoms. Wallace contains no reference to the use of one or more backbone atoms or to the use of geometric constraints between nine or more atoms. Applicants respectfully request that this rejection be reconsidered and withdrawn.

As noted above, none of the amendments to any claims that are the subject of this rejection, or the presentation of new claims, may be interpreted as limiting in any way the scope of any issued claims.

Holm *et al*.

Pending claims 2-14, 16-20, 22, and 44-60 were rejected under 35 USC 102(b) as allegedly anticipated by Holm *et al.* for reasons of record.

With regard to Applicants' statements concerning Holm *et al.*, the Examiner first asserted that the "instant specification defines 'functional site' as any site in protein [sic] that has a function" and maintains that the "definition encompasses an entire protein as well." Notwithstanding other distinctions between Applicants' invention and the Holm *et al.* paper, Applicants note that neither the specification nor any claims, however, refer to an entire protein

with respect to a functional site. They refer atoms within amino acids in a functional site in a protein.

Secondly, the Examiner asserts that the focus of Holm *et al.* "is on the definition and prediction of the functional site descriptors [sic], for example, the amino acid residues present in an enzymatic active site, such as urease." In contrast to this statement, however, Applicants note that Holm *et al.* relates to identification of a large superfamily of proteins that are said to have a similar structurally conserved core. The members of this family were reportedly identified by a combination of structural superposition (of the entire proteins or large domains of the proteins) and analysis of sequence alignments to identify patterns of conserved residues. As specified in the paper (p. 72, second column, bottom), the actual steps reportedly required to accomplish this task were:

1. Structural alignment using Dali, a structure superposition algorithm;
2. Sequence alignment to identify sequences that are similar (a common technique known as "profiling");
3. Analysis of sequence patterns within each family of similar sequences;
4. Correlation of these sequence patterns with sequence patterns in proteins whose structures have previously been identified; and,
5. Threading and 3D model building of sequence neighbors thus identified.

Accordingly, there is nothing in Holm *et al.* that describes the making of a functional site descriptor as described and claimed by Applicants, or the application of such a descriptor to protein structures as described and claimed by Applicants. Indeed, Holm *et al.* makes it very

clear that structural superposition of entire protein structures and sequence signature patterns were essential to their analysis of a structural superfamily. It is plain that structural superposition played a major role in the identification of this structural superfamily because the method identifies proteins that are structurally conserved but non-functional. *See*, *e.g.*, page 79, second column, line three, where it is stated that, "three member families contain branches in which the catalytic residues are not conserved, yet family membership is clear at 30-40% sequence identity with closest neighbors [emphasis added]."

As indicated in the instant case, the invention described and claimed for the creation and application of functional site descriptors does not require structural superposition or analysis of sequence signature patterns. Applicants respectfully request that this rejection be reconsidered and withdrawn.

As noted above, none of the amendments to any claims that are the subject of this rejection, or the presentation of new claims, may be interpreted as limiting in any way the scope of any issued claims.

CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

In accordance with 37 C.F.R. §1.121, a marked up copy of the reworded claims is appended hereto. Additions are noted by underlining. Deletions are noted by bracketing.

If necessary, please apply additional and necessary charges, and apply all credits, to Deposit Account No. 06 1050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Dec. 17, 2002

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3. (Twice amended) The computer program product of claim 53, wherein said [the identity of an] amino acid residues used to define said [specified in the] functional site are [descriptor is] selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val.

5. (Twice amended) The computer program product of claim 53, wherein each geometric constraint within said one or more [the set of] geometric constraints is selected from the group consisting of an atomic position specified by a set of three dimensional coordinates, an interatomic distance, and an interatomic [bond] angle.

6. (Three times amended) The computer program product of claim 5, wherein at least one member of said one or more [the set of] geometric constraints is an atomic position specified by a set of three dimensional coordinates, [wherein] and said three dimensional coordinates [the atomic position can vary within] are associated with a preselected root mean square deviation variance.

8. (Twice amended) The computer program product of claim 5, wherein at least one member of said one or more [the set of] geometric constraints is an interatomic distance.

9. (Twice amended) The computer program product of claim 5, wherein at least one member of said one or more [the set of] geometric constraints is an interatomic [bond] angle [range].

10. (Twice amended) The computer program product of claim 53, wherein said functional site descriptor further comprises [comprising] a conformational constraint.

12. (Twice amended) The computer program product of claim 53, wherein all of the atoms for which geometric constraints are provided [comprise a part of the protein backbone and] are selected from the group consisting of protein backbone [an] α-carbons, [an] amide nitrogens, [a] carbonyl carbons and [a] carbonyl oxygens.

13. (Twice amended) The computer program product of claim 53, wherein at least one of said one or more atoms in said amino acids used to define said functional site is a pseudoatom.

14. (Twice amended) The computer program product of claim 13, wherein the pseudoatom is a center of mass with respect to at least two atoms selected from [the group consisting of an atom from one amino acid residue and an atom from] at least two amino acid residues used to define said functional site [of the protein].

16. (Twice amended) The computer program product of claim 53, wherein the functional site descriptor defines a functional site of a protein corresponding to a [comprising biological] function selected from the group consisting of [a] disulfide oxidoreductase activity, [a] α/β hydrolase activity, [a] phospholipase activity, and [a] T1 ribonuclease activity.

18. (Twice amended) The computer program product of claim 53, wherein the functional site descriptor defines a function [is] selected from the group consisting of an enzyme active site [of an enzyme], a ligand binding domain, and a protein-protein interaction domain.

19. (Twice amended) The computer program product of claim 18, wherein said ligand binding domain binds a ligand selected from the group consisting of a substrate, a co-factor, and an antigen.

22. (Twice amended) The computer program product of claim 20, wherein the library comprises at least two functional site descriptors for [at least] one or more functions of a protein or family of proteins [of the biological functions represented by the library].

45. (Three times amended) A computer program product comprising a computer [useable] readable medium having executable instructions representing a computer program [logic] recorded thereon, said executable instructions comprising a computer program for creating a functional site descriptor [for use in predicting a biological function of a protein], wherein the functional site descriptor identifies a functional site using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site, said functional site corresponding to a function of a protein or family of proteins, said computer program [logic] comprising [computer program code logic configured to perform the operations of]:

(a) program code for determining an amino acid residue identity constraint for each amino acid residue used to define said functional site, wherein said amino acid residue identity constraint for each amino acid residue is a single amino acid residue identity or two or more alternative amino acid residue identities;

(b) program code for determining one or more geometric constraints between at least three different atoms, wherein at least three of said different atoms are in different

amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) program code for assigning a variance to each geometric constraint in order to provide a degree of relaxation for each said geometric constraint; and,

(d) program code for causing a computer to output said constraints comprising functional site descriptor created for said functional site to a storage device or a display device.[:

determining a set of geometric constraints for a functional site associated with a biological function of a protein, wherein a set of geometric constraints comprises one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise:

(i) an atom of a first amino acid residue of the functional site comprising the amino acid residue of part (a), wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon; and

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom, and a pseudoatom, wherein at least one of (i), (ii) or (iii) comprises a backbone atom or a backbone pseudoatom;

(b) modifying one or more geometric constraints of said set of geometric constraints to produce a modified set of geometric constraints,

(c) comparing said modified set of geometric constraints to a data set of functional sites correlated with said biological function to determine whether said modified set of geometric constraints compares positively with said data set of functional sites correlated with said biological function and, if there is a positive correlation; and

(d) repeating said modifying and comparing operations of steps b and c to modify one or more of said geometric constraints of said set of geometric constraints to an extent that said modified set of geometric constraints compares positively with said data set of functional sites correlated with said biological function without encompassing a predetermined amount of data sets not correlated with said biological function.]

48. (Twice amended) The computer program product of claim 45, wherein said set of geometric constraints further comprises one or more geometric constraints with respect to one or more atoms or pseudoatoms of one or more amino acid residues that are adjacent to an amino acid residue used to define said functional site [of said two or more amino acid residues].

49. (Twice amended) The computer program product of claim 45, wherein said set of geometric constraints comprises geometric constraints selected from the group consisting

of an atomic position[s] specified by a set[s] of three dimensional coordinates, an interatomic distance[s], and an interatomic [bond] angle[s].

50. (Twice amended) The computer program product of claim 45, wherein at least one of the geometric constraints of said set of geometric constraints comprises an interatomic distance[s] between [one or more] atoms and/or pseudoatoms [of the amino acid residues of the functional site descriptor].

52. (Twice amended) The computer program product of claim 68 or 69 [45], wherein said operation of modifying one or more geometric constraints of said set of geometric constraints to produce a modified set of geometric constraints comprises:

computing an average value for a geometric constraint within the set of geometric constraints by determining values for said geometric constraint from at least two different proteins having functional sites that correlate with said biological function, and calculating said average value;

computing a standard deviation with respect to such geometric constraint; and

applying a multiplier to said computed standard deviation to generate said modified geometric constraint.

53. (Twice amended) A computer program product [in] comprising a computer readable medium having executable instructions representing a computer program recorded thereon, said executable instructions comprising [encoding] a functional site descriptor, wherein the functional site descriptor defines [at least one] a functional site corresponding to a function of a protein or family of proteins, other than a divalent metal ion binding site, the functional site

descriptor being defined using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site and comprising:

(a) an amino acid residue identity constraint for [a first] each amino acid residue used to define [of the] said functional site, wherein said amino acid residue identity constraint for [the first] each amino acid residue is [identified as] a single amino acid residue identity or [as a set of] two or more alternative amino acid residue[s] identities; [and]

(b) one or more geometric constraints for [between] at least three different atoms, wherein at least three of said different atoms [each atom is] are in [a] different amino acid residues of the protein used to define said functional site and [the different atoms comprise] at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen; and,

(c) each geometric constraint is associated with a variance in order to provide a degree of relaxation for each said geometric constraint.[:

(i) an atom of the first amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a

backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon; and

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom, and a pseudoatom, wherein at least one of (i), (ii) or (iii) comprises a backbone atom or a backbone pseudoatom.]

54. (Twice amended) A computer implemented method for determining a functional site descriptor, wherein the functional site descriptor [that] defines a [spatial configuration of a] functional site[, wherein the functional site descriptor defines a functional site] corresponding to a function of a protein or family of proteins other than a divalent metal ion binding site, the [method] functional site descriptor being defined using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site, comprising the following steps:

(a) identifying an amino acid residue identity constraint for [a first] each amino acid residue used to define [of the] said functional site, wherein said amino acid residue identity constraint for [the first] each amino acid residue is [identified as] a single amino acid residue identity or [as a subset of] two or more alternative amino acid residue[s] identities; [and]

(b) identifying one or more geometric constraints for [between] at least three different atoms, wherein at least three of said different atoms [each atom is] are in [a] different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or

more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen [the different atoms comprise:

(i) an atom of the first amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon; and

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom,

wherein at least one of (i), (ii) or (iii) comprises a backbone atom or a backbone pseudoatom, thereby determining a functional site descriptor]; and,

(c) providing a variance for association with each geometric constraint in order to provide a degree of relaxation for each said geometric constraint.

56. (Twice amended) A computer-implemented method for defining a functional site descriptor [of a protein], wherein the functional site descriptor defines a functional site corresponding to a function of a protein or family of proteins, the functional site descriptor being defined using at least one atom from each of about fifteen or fewer amino acid residues used to define said functional site, comprising the following steps:

(a) identifying an amino acid residue identity constraint for [a first] each amino acid residue used to define [of the] said functional site, wherein said amino acid residue identity constraint for [the first] each amino acid residue is [identified as] a single amino acid residue identity or [as a subset of] two or more alternative amino acid residue[s] identities; [and]

(b) identifying one or more geometric constraints for [between] at least three different atoms, wherein at least three of said different atoms [each atom is] are in [a] different amino acid residues of the protein used to define said functional site and at least one of said atoms is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, and a pseudoatom comprised of two or more of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, and a backbone carbonyl oxygen [the different atoms comprise:

(i) an atom of the first amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom, and a beta-carbon; and

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom,

wherein at least one of (i), (ii) or (iii) comprises a backbone atom or a backbone pseudoatom, thereby determining a functional site descriptor]; and,

(c) providing a variance for association with each geometric constraint in order to provide a degree of relaxation for each said geometric constraint.

58. (Amended) A computer system, comprising:

(a) a processor; and

(b) a computer program product as set forth in claim 45 [or claim 57].

59. (Amended) A computer system, comprising:

(a) a processor; and

(b) a computer program product as set forth in claim 53.

New claims 61 to 116 have been added.